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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/618,183 | 07/10/2003 | Stephen Epstein | MEDIV2010-4 | 4304 |
| 28213 | 7590 | 12/15/2004 | EXAMINER | |
| GRAY CARY WARE & FREIDENRICH LLP 4365 EXECUTIVE DRIVE SUITE 1100 SAN DIEGO, CA 92121-2133 | | | AKHAVAN, RAMIN | |
| | | ART UNIT | PAPER NUMBER | |
| | | 1636 | | |

DATE MAILED: 12/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

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|------------------------------|------------------------|---------------------|--|
| Office Action Summary | Application No. | Applicant(s) | |
| | 10/618,183 | EPSTEIN ET AL. | |
| | Examiner | Art Unit | |
| | Ramin (Ray) Akhavan | 1636 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 09/23/2004.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1,2,4-9,13-27,29-43,45 and 46 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1,2,4-9,13-27,29-43,45 and 46 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) Notice of Informal Patent Application (PTO-152)
- 6) Other: _____

DETAILED ACTION

Acknowledgment is made of a response/amendments, filed 09/23/2004, as well as a Terminal Disclaimer. Claims 3, 10-12, 28 and 44 are cancelled. All rejections not repeated herein are hereby withdrawn. Claims 1-2, 4-9, 13-27, 29-43 and 45-46 are pending and under consideration in this action. As no new grounds of rejection are set forth that are not necessitated by material amendments to the claims, **this action is made Final.**

Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. **Claim 1-2, 4-9, 13-27, 29-43 and 45-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of hind-limb ischemia in mice, does not reasonably provide enablement for promoting angiogenesis in any tissue/organ of any animal or heart/limb tissue in a human patient.**

This ground of rejection is of record and repeated herein. A response to Applicant's arguments is set forth immediately following the body of this rejection. (Infra, Response to Arguments). The claims have been amended to delimit the transfection vector to adenovirus. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The test for enablement is whether one skilled in the art could make use the claimed invention from the disclosure in the specification coupled with information known in the art

without undue experimentation. *United States v Teletronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor but instead is a conclusion reached by weighing many factors which are outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

The factors include the following:

Scope/Breadth of the claims. The claims are drawn method promoting development of collateral blood vessel formation in a patient where autologous bone marrow cells (ABM) that are transfected early attaching cells, which are transfected with an adenovirus vector encoding hypoxia inducing factors-1 (HIF-1), endothelial PAS domain protein 1 (EPAS1), Monocyte Chemoattractant Protein 1 (MCP-1), granulocyte-monocyte colony stimulating factor (GM-CSF), PR39, fibroblast growth factor or nitric oxide synthase (NOS). In addition, composition claims are limited as “therapeutic” and are directed to said transfected early attaching cells. In addition the claims are directed to enhancing collateral blood vessel formation in any site *in vivo* (i.e. base claim 1), into heart or limb tissue (i.e. base claims 17 and 18). Furthermore, ABMs can be transfected with nucleic acids obtained from any source to express the articulated factors (Supra, e.g. NOS or PR39) with the expectation of enhanced angiogenesis.

Nature of the invention. All claims are directed to treatment, insofar as issues of enablement are concerned. For example, the method claims recite the term “patient”, which reads on a human patient. While the composition claims recite the limitation “therapeutic”. The specification discloses that the claimed method or composition find particular use in gene therapy applications in a human patient.

Furthermore the encompassed methods and compositions, insofar as they are delimited to adenoviral transfected early attaching ABMs, are drawn to gene therapy. In addition, because the conditioned medium alone can also contain adenoviral vectors, administration of such medium also reads on delivery of such vectors, which necessarily reads delivery of adenoviral vectors encoding the various target proteins.

Sate of the art/Unpredictability of the art. The specification does not teach *how to use* the claimed methods and composition therapeutically commensurate with the scope of the claims for the following reasons. There is a substantially high level of unpredictability in the art of gene therapy. At the time the application was filed, the art of delivering transduced cells to an individual with the aim of producing therapeutic products so as to achieve a desired outcome was poorly developed and unpredictable. In a review article published in Nature in 1997, Inder Verma states, “Although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still not single outcome that we can point to as a success story.” (*Infra*, at p. 239). Gene therapy is a highly unpredictable art with poor efficiency of delivery of the transgene to the target cells, poor transformation efficiency of target cells, unpredictable and transient expression of the transgene in target cells, etc. (See Kmiec, American Scientist, 1999, Vol. 87: 240-147; Anderson, Nature, 1998, Vol. 392: 25-30; Verma et al., Nature, 1997, Vol. 389: 239-242; reviewing the multitude of difficulties and lack of success in gene therapy methods). (See, Juengst, ET. June 200, BMJ, 3326:1410-11; noting, “Gene transfer...makes change in a cellular ecosystem that will almost always be pleiotropic in its effects, and often in unpredictable ways”.) Such concerns are evident even today. (*Infra*, St. George. Gene Therapy, 2003; 10:1135-1141).

Furthermore, insertional mutagenesis, which may occur via viral vectors such as adenovirus, “will ramify through the cellular proteome in multiple directions, depending on how the modified coding region [i.e. in the now mutated gene] is used by the cell.” (Juengst, 2003, p. 1410, col. 2, ¶ 2). Additionally, gene vectors, including adenoviral vectors, used to deliver constructs encoding therapeutic products may be erroneously inserted into a particular gene resulting in unknown, adverse or detrimental effects. (See, Check, Erika, Feb. 13, 2003, Nature, 421: 678; citing occurrence of leukemia due to insertion of retroviral vectors used in gene therapy into a particular stretch of DNA); (see also, Juengst. June 2003, indicating that gene transfer often has multiple and unpredictable effects on cells).

The claimed methods and composition encompass a wide variety of different therapeutic genes and further encompass producing angiogenesis in virtually any region or tissue in the body. More particular embodiments that are limited to heart or limb tissue, encompass adenoviral expression of functionally distinct proteins. (e.g. NOS, MCP-1 or PR39). Even the most promising areas present barriers to successful gene therapy that could not be overcome with routine experimentation. For example, in the area of angiogenesis in the heart, additional mechanistic and transactional pre clinical investigations are essential, and well-designed studies are required before the great potential of adult stem cell therapy can be fully realized. (Chiu RC. Exp.Opin. Biol. Ther.; 3(2):215-25, 2003, e.g. Abstract; see entire reference). More particularly, with respect to gene therapy, the transduced cells in a human patient would need to express the angiogenic factor for a threshold period of time to promote angiogenesis (e.g. strength of expression from the promoter), especially where the ABMs are *impaired* due to an underlying

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condition (i.e. claim 1). Therefore a relevant animal model would have to address problems of poor or transient expression *in vivo*.

Moreover, "All gene therapy designed to potentiate local angiogenesis carries the theoretical risk that pathological angiogenesis at a remote site could be stimulated, ie, ocular angiogenesis or tumor angiogenesis." (Folkman, J. Circulation; 87:1108-1110 (1998); see p. 1108, col. 2). In addition, ABMs transfected with adenoviral vectors would at least to some extent express viral proteins, which may induce a deleterious immune response in a human patient.

Even current understanding of myogenic stem cell transplantation, including utilizing gene therapy notes, "With respect to the ultimate clinical utility of myocyte and myogenic stem cell transplantation, it is important to recognize that we are still very early in the game." (e.g. Dowell et al. 2003. Cardio. Res., 58:336-350 at p. 347, col. 2). Therefore clearly the state of the art is in the nascent stage of development and there are many concerns with expression inefficiency and unpredictability with respect to *in vivo* applications. Such obstacles are not addressed in the instant specification, thus obviating routine practice of the claimed invention. Moreover, such obstacles should not be construed as safety concerns, but rather, as indicators of unpredictability that obviate the invention's use without undue experimentation. The instant specification does not adequately teach one skilled in the art *how to use* the claimed invention for *in vivo* therapy in a human patient, where transduced ABMs are either administered at any location in the body where angiogenesis is deemed needed or to heart and limb tissue.

Amount of guidance provided. There is some generic guidance provided, but no significant relevant guidance is provided with respect to gene therapy or transfection of ABMs and treatment of a human patient.

Number of working examples. A single working example is provided that encompasses direct administration of murine bone marrow cells, which are transfected with adenovirus encoding HIF-1 α /VP16, directly into an ischemic limb of syngeneic mice. This result is not necessarily predictive of success in *any* organ/tissue, or in administration into heart and limb tissue of a human patient, for example.

Amount of Experimentation Required. The level of skill in the art required to practice the claimed invention is high. However, given the unsolved hurdles and obstacles to successful practicing of the invention, the level of unpredictability in the art and limited relevance of working examples as related to the obstacles presented, it must be considered that the skilled artisan would be required to conduct trial and error experimentation of an undue nature in order to attempt to practice the claimed invention commensurate with the scope of the claims.

Response to Arguments

At the outset it should be noted that Applicant makes reference to post-filing studies as reflected in three publications, but there are no copies or attachments present as indicated. (Remarks, p. 12 bridging to p. 13). Applicant's arguments are summarized as asserting that certain references do not reflect the state of gene therapy (Remarks, p. 10), transfection of ABMs or continued expression of therapeutic genes is not necessary to promote collateral blood vessel formation (Remarks, p. 11), that the disclosure if enabling for mice ischemic limb should also be enabling for administration to heart tissue and human heart (Remarks, p. 12), that post-filing

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publications show that ABMs or conditioned medium administered to heart or limb tissue promote angiogenesis (Remarks, pp. 12-13) and above all, that there is not need for transdifferentiation of ABMS into particular cell types or for continued expression of transgenes. (Remarks, p. 13). Each of the arguments will be addressed in turn.

First, with respect to the Verma and Anderson references, these articles point out obstacles and unpredictability related to gene transfer, which are of concern even today. Indeed, the additional references (e.g. Juengst, 2003; Check, 2003) bear this point out. Furthermore, as a result of material changes to the claims delimiting ABMs' transduction via adenoviral vectors (Ad vectors), an additional reference is provided that outlines some of the obstacles with using Ad vectors. (See, St. George. Gene Therapy. 2003; 10:1135-1141; see entire document ; p. 1136, col. 1 , noting that the toxicity associated with Ad vectors is extremely complex involving both the innate and adaptive immune response). Since Ad vector toxicity can be host-dependent, a mouse model would not necessarily be predictive of toxicity observed in a human patient. (Id. at p. 1136, col. 1, ¶ 1, bottom; noting that it is important to consider the lack of correlation between animals naïve to adenovirus and patients that are not likely similarly naïve). While Ad vector administration can be distinguished from administration of cells containing Ad vectors, ABMs can certainly release Ad vectors into the target tissue or systemic environment. It is noted that there are not teachings in the specification with respect to viral titers. Furthermore, as indicated in the enablement rejection of record, Ad vectors will invariably express viral proteins, an immune response to which could be lethal in the host. (Id., col. 2, last ¶). Moreover, when choosing an animal model, it is noted that primates are most instructive to understanding Ad-mediated toxicity. (Id., col. 1, ¶ 2).

Furthermore, pretreatment of animal models with steroids to reduce Ad-toxicity has been shown to reduce cytokine expression (Id., ¶3), thus such a step cannot be used routinely to obviate immune toxicity concerns where cytokine/chemokine expression is required. In sum, to date, the state of art of gene therapy still faces many obstacles that would require undue experimentation, where the instant disclosure does not address such obstacles.

Applicant's next assertion is that transfection of ABMs is not necessary to achieve the objective for promoting collateral blood vessel formation. However, such an assertion simply ignores the fact that the claims are drawn to transfected ABMs. Therefore, this argument is based on limitations that are not claimed. A related contention is that ABMs or conditioned medium from ABM cultured *ex vivo*, independent of transfection, can promote angiogenesis. This may be true, but as noted previously, the claims are directed to adenoviral-transfected ABMs or media in which transfected cells are grown. Therefore, concerns with Ad vector-related toxicity are not present where transfection with Ad vectors is not involved.

In addition, Applicant asserts that post-filing art shows that the instant disclosure is enabling for the full scope of the claims. However, this assertion is not tenable considering the post-filing art does not involve transduced ABMs or conditioned media from transduced cells. Although copies of the documents referred to are not provided, based on examination of the relevant art it is presumed that Applicant is not referring to post-filing art using Ad vectors in expressing angiogenic factors for *in vivo* therapeutic application in humans to promote angiogenesis. As noted above, a murine model cannot be deemed predictive for Ad vector-related toxicity that could occur in humans, thus a murine model for hind limb ischemia would

not necessarily obviate undue experimentation with respect to administration of transduced cells medium from transduced cells to the human heart or human limb tissue.

Finally, in addressing transient expression problems in gene therapy, Applicant asserts that continued expression is not necessary to obtain the therapeutic objective of the invention. Notwithstanding concerns with viral-related toxicity, expression levels would have to be meet a threshold level to mete out therapeutic effects. Because there is little significant relevant guidance provided in the specification and such means of therapy is not routinely practice in the art, one of skill would have to undertake significant and undue experimentation to evaluate expression levels for a particular therapeutic protein. Furthermore, such evaluation would have to be undertaken with the overarching and unpredictable concerns with respect to Ad viral-related toxicities. In sum, Applicant's arguments have been considered but are not deemed persuasive.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action.

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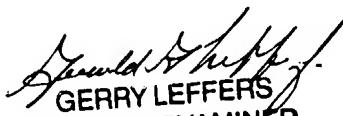
In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ray Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached between 8:30-5:00, Monday-Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD, can be reached on 571-272-0781. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully submitted,

Ray Akhavan/AU 1636


GERRY LEFFERS
PRIMARY EXAMINER